

MIS-A can occur after the acute phase of SARS-CoV-2 infection. The only symptom at the time of infection was olfactory disturbance, which is similar to other case reports of MIS-A occurring in asymptomatic or minimally symptomatic patients (5).

It has been reported that MIS-A can cause symptoms similar to those of Kawasaki disease (6). This case did not meet the American College of Cardiology criteria for Kawasaki disease (7) but did meet the definition of incomplete Kawasaki disease. Conjunctivitis persisted for 4 weeks after the onset of MIS-A and gradually improved.

In February 2021, a case definition was proposed for reporting cases of multisystem inflammatory syndrome in adults and children after vaccination (8). Considering the possibility that the disease develops after asymptomatic SARS-CoV-2 infection and that increased IgG levels can be involved, MIS-A is rare, but the disease concept of MIS-A should be widely acknowledged. Clinicians should consider obtaining detailed history and examining SARS-CoV-2 IgG levels for cases of severe inflammatory disease with unexplained cardiac decompensation.

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Changing Molecular Epidemiology of Hepatitis A Virus Infection, United States, 1996–2019

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Hepatitis A virus (HAV) genotype IA was most common among strains tested in US outbreak investigations and surveillance during 1996–2015. However, HAV genotype IB gained prominence during 2016–2019 person-to-person multistate outbreaks. Detection of previously uncommon strains highlights the changing molecular epidemiology of HAV infection in the United States.

Hepatitis A virus (HAV) is transmitted primarily through person-to-person contact or exposure to contaminated food or water. After the introduction of hepatitis A vaccine recommendations in the United States in 1996, reports of hepatitis A cases decreased progressively from 1999 to 2011 by a total of $\approx 95\%$ (1,2). However, we recently showed that hepatitis A cases increased 294% during 2016–2018 compared with 2013–2015 among persons who use drugs (injection or noninjection), persons experiencing homelessness, or men who have sex with men (3,4).

HAV strains infecting humans are genetically classified into genotypes I, II, and III. Genotype I is further divided into subtypes A, B, and C, and genotypes II and III are divided into subtypes A and B. In this study, we investigated HAV genotype and strain distributions in the United States during 1996–2019.

Genetic testing was performed by using DNA sequencing, and we included HAV sequences obtained from 9,203 specimens collected during outbreak investigations and surveillance activities conducted by the Centers for Disease Control and Prevention (CDC) or state health departments during 1996–2019 (Appendix Table, <https://wwwnc.cdc.gov/EID/article/27/6/20-3036-App1.pdf>). We performed phylogenetic analysis of a 315 base-pair fragment of the HAV viral protein 1–amino terminus of 2B genomic region amplified from serum specimens (Appendix Figure 1).

We found that during 1996–2015, HAV genotype IA was most common among specimens collected through

surveillance (93%; 1,587/1,706) and outbreak investigations (84.4%; 706/836); genotype IB was detected among only 6.4% (110/1,706) of surveillance and 15.2% (127/836) of outbreak specimens. Genotype IIIA was detected in $\leq 0.5\%$ of both collections (Table). During 2016–2019, a total 6,661 outbreak specimens were collected from many states across the country (Appendix Figure 2). Sequences from these outbreaks represented $\approx 19\%$ of all HAV cases reported to CDC through the National Notifiable Diseases Surveillance System (4), ≈ 3 times more specimens than were collected during 1996–2015. Among the 6,661 specimens collected during 2016–2019, genotype IA was identified in 15.7% of specimens, IB in 82.8%, and IIIA in 1.5% (Table).

Among all 9,203 tested specimens, we identified 1,055 HAV strains that we defined as having unique genetic variants; 352 (33.4%) HAV strains were identified from specimens collected during 2016–2019 (Figure). Genetic analyses demonstrate that 63.4% ($n = 102$) of genotype IB strains and 40% ($n = 6$) of genotype IIIA strains identified during 2016–2019 belonged to 2 large genetic clusters or groups of closely related HAV strains (Figure), but genotype IA strains were distributed among many small genetic clusters.

The CDC-developed Global Hepatitis Outbreak and Surveillance Technology (GHOST) system improved molecular testing capabilities of state and local health departments during the 2016–2019 multistate outbreaks. Molecular epidemiologic methods have helped clarify HAV transmissions within networks of persons with similar risk factors (5). By using genetic testing, CDC has assisted in 25 outbreak investigations associated with a common source transmission by contaminated food (6,7) and person-to-person transmissions (8,9).

For 20 years (1996–2016), during the national decrease in HAV cases attributed to increased vaccination, genotype IA was the most detected genotype. However, genotype IB cases associated with

Table. Genotype distribution of HAV specimens collected through surveillance programs and outbreak investigations, United States, 1996–2019*

| Year | No. (%) HAV surveillance specimens † | | | | No. (%) HAV outbreak specimens ‡ | | | | No. (%) HAV specimens | | | |
|-----------|--------------------------------------|-----------------|--------------|---------|----------------------------------|-----------------|-----------------|-------------|-----------------------|-----------------|-----------------|-------------|
| | Total | IA | IB | IIIA | Total | IA | IB | IIIA | Total | IA | IB | IIIA |
| 1996–2015 | 1,706 | 1,587 (93.0) | 110 (6.4) | 9 (0.5) | 836 | 706 (84.4) | 127 (15.2) | 3 (0.4) | 2,542 | 2,293 (90.2) | 237 (9.3) | 12 (0.5) |
| 2016–2019 | | ND | | | 6,661 | 1,046 (15.7) | 5,518 (82.8) | 97 (1.5) | 6,661 | 1,046 (15.7) | 5,518 (82.8) | 97 (1.5) |

*Since 2014, the United States has not had established HAV surveillance programs in place to provide specimens for molecular testing of surveillance cases. Specimens collected as part of outbreak investigations during 2016–2019, might include some sporadic cases. During 1996–2015, ≈ 130 HAV specimens/year were tested; During 2016–2019, 1,660 specimens/year were tested. HAV, hepatitis A virus; ND, no data.

†Surveillance specimens tested by the Centers for Disease Control and Prevention (CDC) during 1996–2013 included sentinel county surveillance ($n = 1,234$) during 1996–2006; the Emerging Infectious Disease Program ($n = 418$) during 2007–2013; and the Border Infectious Disease Surveillance ($n = 54$) system during 2007–2013.

‡Outbreak specimens sequenced during 1996–2015 ($n = 836$) were tested by CDC. Outbreak specimens sequenced during 2016–2019 ($n = 6,661$) included data from CDC testing ($n = 5,068$) and data captured through technical assistance offered to sites, which included data from Sanger sequences reported to CDC for technical assistance and analysis from state and local public health laboratories ($n = 341$) and the Food and Drug Administration ($n = 3$); data from ultradeep sequencing and submission to the Global Hepatitis Outbreak and Surveillance Technology portal by state and local public health laboratories ($n = 1,249$).

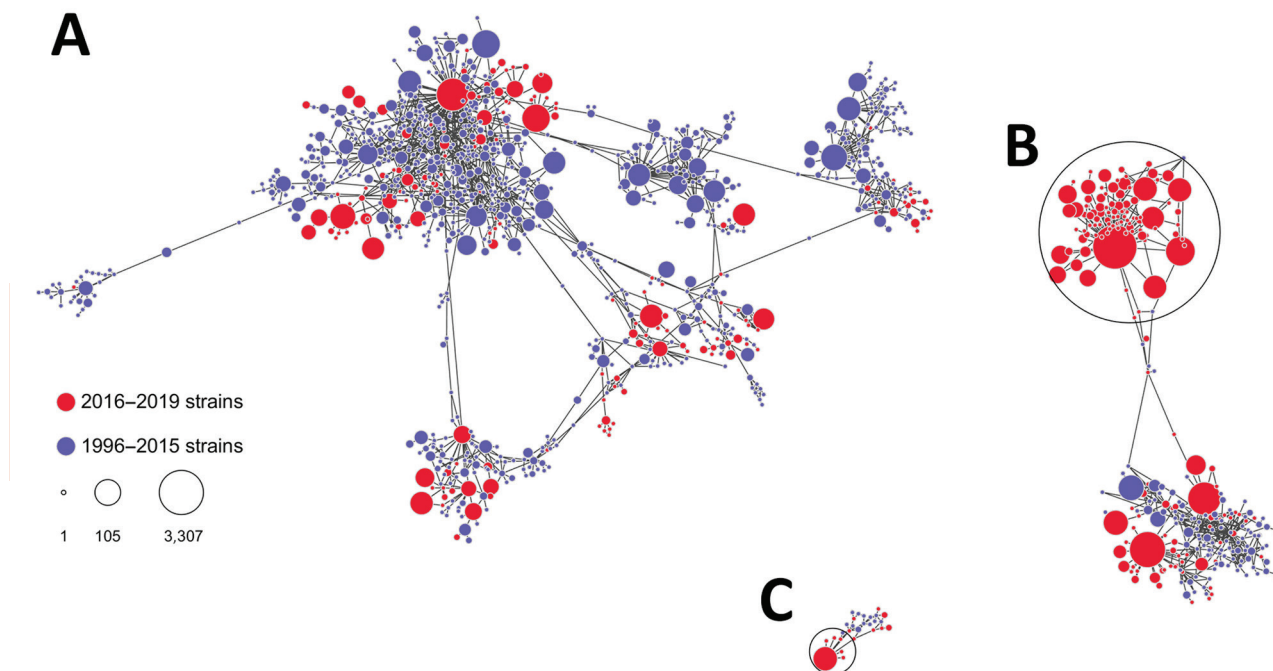


Figure. Genetic relatedness among hepatitis (HAV) strains, United States, 1996–2019. A) IA strains; B) IB strains; C) IIIA strains. Nodes represent HAV strains, and the size of node is proportional to the frequency of the strain; larger nodes denote more frequent detection. Distance between nodes approximates genetic closeness of HAV strains. Genetic clusters of closely related HAV strains encompassing a large fraction of all strains in HAV genotypes IB and IIIA are circled. Visualization created by using Gephi software (<https://gephi.org>).

outbreaks in multiple states increased during 2016–2019. During that time, IB became the most common genotype, detected in 83% of specimens collected across many states (Appendix Figure 2).

Findings from the National Health and Nutrition Examination Surveys during 1999–2012 revealed that despite the overall increase in HAV antibody among children, prevalence of HAV antibody among US-born adults was low (24%), indicating decreasing immunity to HAV (10). However, our molecular data indicate that the increase in number of HAV cases observed in outbreaks during 2016–2019 might not be attributable solely to the decline in the population's HAV immunity. Because HAV genotype IA was dominant in the United States for years, the large person-to-person outbreaks during 2016–2019 reasonably could be expected to be caused by genotype IA strains widely circulating in the country, but our genetic analysis shows predominance of the previously rare HAV genotype IB strains. Identification of 1 large cluster and several small genetic clusters suggests ≥ 1 introduction of genotype IB to the affected population in multiple states during 2016–2019. On the basis of these findings, we hypothesize that genotype IB was introduced from regions of the world where these strains are endemic and could be responsible

for initiation of the outbreaks among vulnerable populations (Appendix Figure 3). GHOST was instrumental in identifying changes in molecular epidemiology of HAV infections and is an example of novel emerging technologies that can be used for national viral hepatitis molecular surveillance program.

Our observations are hallmarks of a change in HAV molecular epidemiology in the United States. GHOST technology is improving hepatitis detection at the state and local level. Our findings emphasize the need for systematic HAV surveillance for strain characterization, timely detection of transmission clusters, and assistance in guiding public health interventions and vaccination efforts.

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Molecular Typing of *Burkholderia mallei* Isolates from Equids with Glanders, India

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Changing Molecular Epidemiology of Hepatitis A Virus Infection, United States, 1996–2019

Appendix

Study Methodology

The study included available immunoglobulin M (IgM) anti-hepatitis A virus (HAV)–positive serum specimens ($n = 1,706$) collected by Centers for Disease Control and Prevention (CDC) surveillance programs during 1996–2013; 836 specimens tested by CDC from 23 outbreak investigations during 2002–2015; and 6,661 specimens associated primarily with person-to-person outbreaks in the United States during 2016–2019 (Appendix Table) (1,2). Genetic testing of specimens collected across all states was performed by using DNA sequencing and phylogenetic analysis of a 315 nt region, at position of 2897–3288 of the HAV genome (Appendix Figures 1-3). Until January 2018, only 1 sequence per specimen was obtained by using Sanger sequencing (3). In February 2018, CDC implemented ultradeep sequencing (UDS) for HAV as part of Global Hepatitis Outbreak and Surveillance Technology (GHOST; 4), which resulted in sequencing multiple HAV sequence variants from each specimen. HAV genotyping was conducted by using either a single sequence obtained by Sanger sequencing or the most frequent sequence obtained from each specimen by UDS. These sequences were used to represent strains, defined as unique genetic variants, and to identify genetic clusters. Since 2017, as part of technical assistance offered by CDC, state laboratories reported 341 Sanger sequences and the U.S. Food and Drug Administration (FDA) reported 3 from food sources. UDS data from 1,249 specimens were submitted to CDC by state and local health laboratories through GHOST as part of outbreak investigations during 2018–2019.

Study Limitations

A limitation of this study is that 81.5% of the tested specimens were collected from HAV outbreak investigations that occurred during 2002–2019 and 18.5% of specimens was collected from routine surveillance activities that occurred during 1996–2013, which represented only 1% of the total reported HAV cases. Owing to the unprecedented magnitude of the 2016–2019 person-to-person outbreaks (4), genetic testing of specimens was not completely proportional to the number of cases reported from each state and includes a small proportion from other outbreaks and sporadic cases. Thus, the identified change in genotype predominance likely is not generalizable to all hepatitis A cases in the United States and is weighted toward the genotypes associated with the ongoing outbreaks (4). The study included available remnant convenient serum specimens obtained within 6 weeks of the onset of symptoms from confirmed cases that tested IgM anti-HAV–positive by the state health departments. HAV strains from deidentified IgM-positive specimens were sequenced at CDC, and independent genetic testing also was conducted by some state health departments by using the CDC-developed UDS assay and GHOST. Despite these limitations, genetic data from the available surveillance and outbreak cases are valuable to describe the changing molecular epidemiologic pattern of viral hepatitis in the United States.

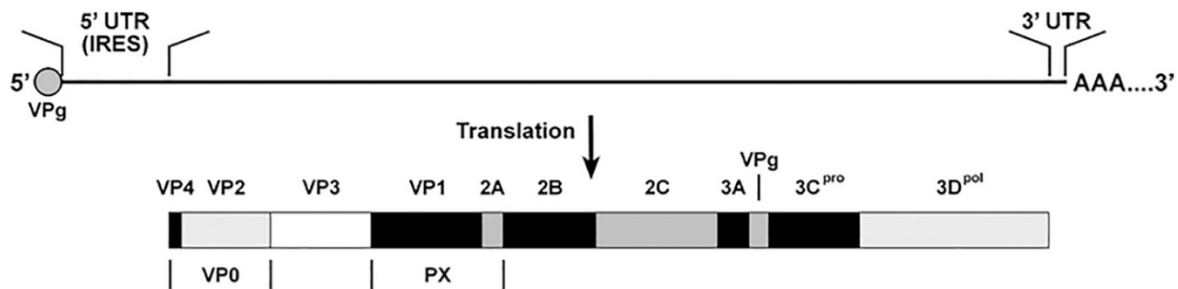
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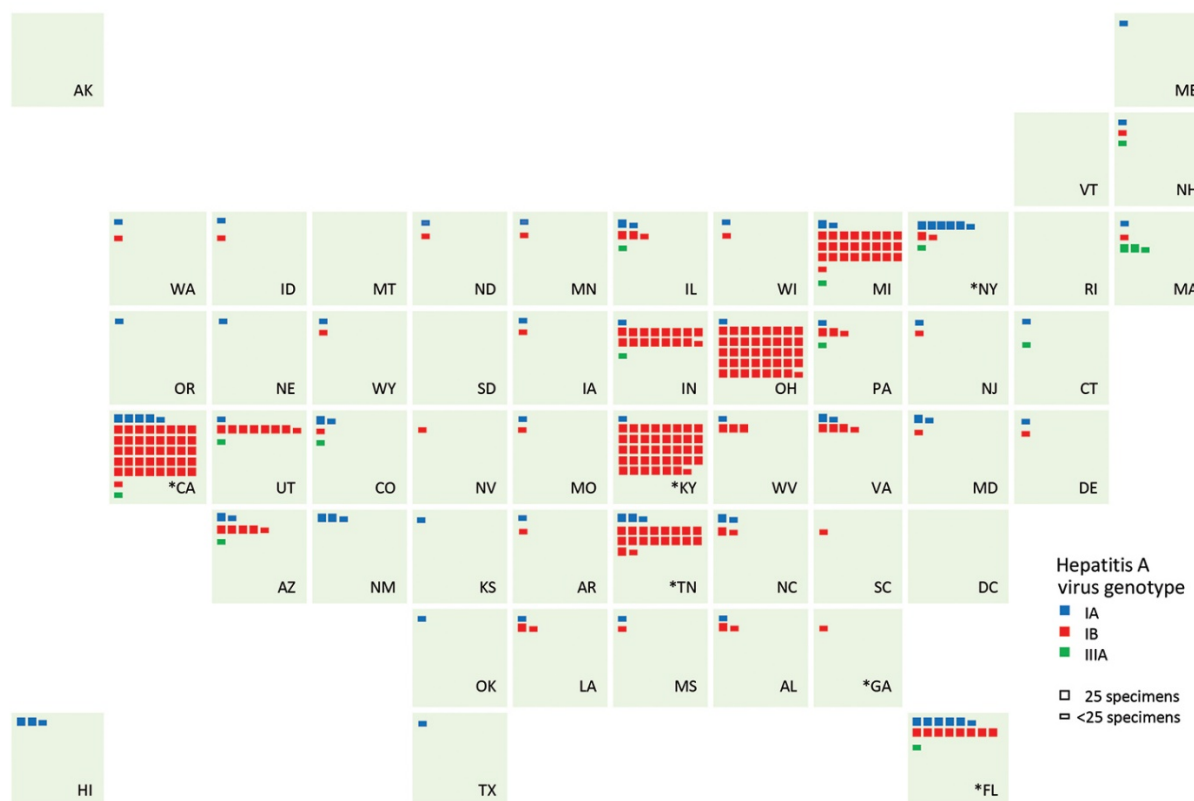
Appendix Table. Details of molecular testing of hepatitis A virus specimens collected through surveillance programs and outbreak investigations, United States, 1996–2019*

| Specimen source | Study period | RNA-positive/tested specimens (%) | Unique genotypes/RNA-positive specimens (%) |
|----------------------------------------------|--------------|-----------------------------------|---------------------------------------------|
| Surveillance system | | | |
| Sentinel Counties Program | 1996–2006 | 1,234/1,510 (81.72) | 403/1,234 (32.66) |
| Binational Border Infectious Disease Program | 2000–2005 | 54/70 (77.14) | 22/54 (40.74) |
| Emerging Infections Program | 2007–2013 | 418/685 (61.02) | 248/418 (59.33) |
| Outbreak investigations* | | | |
| Outbreaks | 2000–2015 | 836/1018 (82.12) | 99/836 (11.84) |
| Outbreaks, person-to-person | 2016–2019 | 6,661/7152 (93.13) | 352/6,661 (5.28) |
| Total | 1996–2019 | 9,203/10,435 (88.19) | 1,055/7,497 (14.07) |

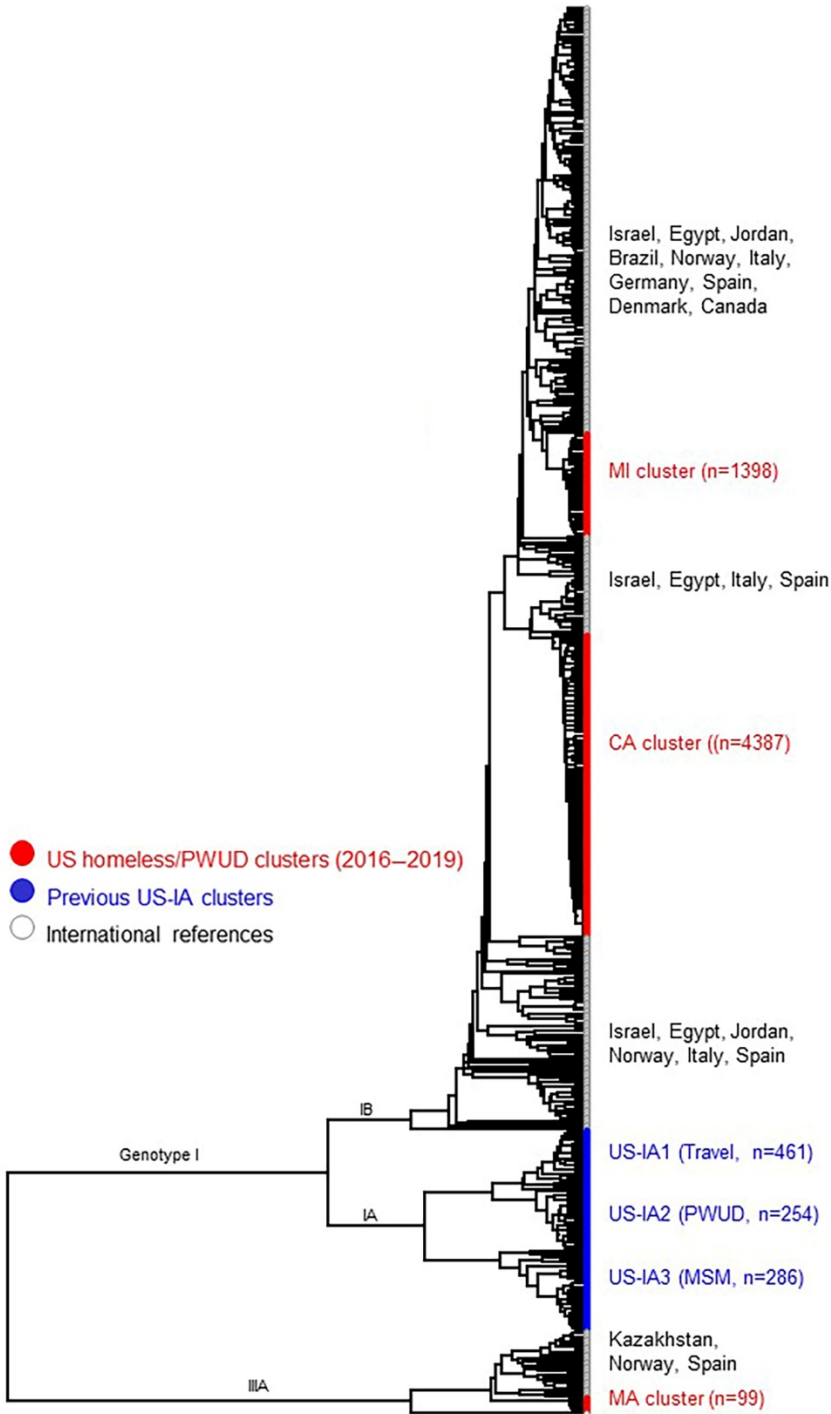
*Specimens tested during 2000–2015 were collected from 23 outbreak investigations. Specimens tested during 2016–2019 were primarily associated with the person-to-person outbreaks; 19% of all cases reported to the Centers for Disease Control and Prevention through the National Notifiable Disease Surveillance System (2).



Appendix Figure 1. Hepatitis A virus (HAV) genome and viral protein 1–amino terminus of 2B (VP1–P2B) genomic region used for DNA sequencing of HAV, United States, 2015–2019. HAV was amplified from serum specimens and genetic testing was performed by using DNA sequencing. We performed phylogenetic analysis of a 315 base-pair fragment of the HAV genome and VP1–P2B region at positions 2897–3288.



Appendix Figure 2. Capacity building and geographic distribution of hepatitis A virus (HAV) genotypes, United States, 2016–2019. In the tile grid map, each tile represents a state, arranged to represent an approximate geographic state location. Color-coded waffle charts embedded in each tile correspond to HAV genotype. The geographic distribution of HAV samples sequenced during 2016–2019 ($n = 6,605$) include ultradeep sequence data acquired through site testing and submitted to the Global Hepatitis Outbreak and Surveillance Technology (GHOST) portal ($n = 1,249$) and consensus Sanger sequence data ($n = 344$) reported by state health departments. Specimens without state assignment ($n = 56$) were not included. Asterisks indicate capacity building in state and local health departments in KY, TN, FL, NY, GA, and San Diego County, CA since 2018 that facilitated independent testing of HAV outbreaks by using GHOST. Sanger sequencing technical assistance was provided to state health laboratories in MI, CA, MN, and FL; and to laboratories of the U.S. Food and Drug Administration. AK, Alaska; AL, Alabama; AR, Arkansas; AZ, Arizona; CA, California; CO, Colorado; CT, Connecticut; DC, District of Columbia; DE, Delaware; FL, Florida; GA, Georgia; HI, Hawaii; IA, Iowa; ID, Idaho; IL, Illinois; IN, Indiana; KS, Kansas; KY, Kentucky; LA, Louisiana; MA, Massachusetts; MD, Maryland; ME, Maine; MI, Michigan; MN, Minnesota; MO, Missouri; MS, Mississippi; MT, Montana; NC, North Carolina; ND, North Dakota; NE, Nebraska; NH, New Hampshire; NJ, New Jersey; NM, New Mexico; NV, Nevada; NY, New York; OH, Ohio; OK, Oklahoma; OR, Oregon; PA, Pennsylvania; RI, Rhode Island; SC, South Carolina; SD, South Dakota; TN, Tennessee; TX, Texas; UT, Utah; VA, Virginia; VT, Vermont; WA, Washington; WI, Wisconsin; WV, West Virginia; WY, Wyoming.



Appendix Figure 3. Hepatitis A virus (HAV) reference sequences were used to investigate HAV genotype distribution in the United States. Sequences used for the phylogenetic tree analysis were 315 bp in length from the viral protein 1–amino terminus of 2B (VP1–P2B) genomic of HAV. PWUD, persons who use drugs (injection or non-injection); MSM, men who have sex with men.